Thyroid hormone (TH) is essential for the proper development of numerous tissues, notably the brain. TH acts mostly intracellularly, which requires transport by TH transporters across the plasma membrane. Although several transporter families have been identified, only monocarboxylate transporter (MCT)8, MCT10 and organic anion-transporting polypeptide (OATP)1C1 demonstrate a high degree of specificity towards TH. Recently, the biological importance of MCT8 has been elucidated. Mutations in MCT8 are associated with elevated serum T3 levels and severe psychomotor retardation, indicating a pivotal role for MCT8 in brain development. MCT8 knockout mice lack neurological damage, but mimic TH abnormalities of MCT8 patients. The exact pathophysiological mechanisms in MCT8 patients remain to be elucidated fully. Future research will probably identify novel TH transporters and disorders based on TH transporter defects.

Introduction

TH exerts its actions on virtually all tissues of mammals. The major biologically active TH is 3,3',5-triiodothyronine (T3), which is generated from the prohormone thyroxine (3,3',5,5'-tetraiodothyronine, T4) by the deiodinating enzymes D1 and D2 [1]. The deiodinase D3 inactivates T4 to 3,3',5,5'-triiodothyronine (rT3) and T3 to 3,3'-diiodothyronine (T2) [1]. The genomic actions of T3 are mediated by nuclear T3 receptors (TRs) [2]. Because the active sites of the deiodinases and the TRs are located intracellularly, TH metabolism and action require transport of the hormone from extracellular compartments (e.g. the bloodstream) across the plasma membrane. Based on their lipophilic nature, it was assumed previously that translocation of iodothyronines across the lipid bilayer of cell membranes occurred by diffusion. However, experimental evidence over the last three decades and clinical studies in recent years show clearly that TH traverses the cell membrane mainly through transporters [3–6]. This review will focus on the molecular characterization of TH transporters. Particular attention will be paid to monocarboxylate transporter 8 (MCT8) and its role in disease.

Molecular characterization of TH transporters

Several observations have indicated that TH uptake has different characteristics across cell types, with regard to ligand specificity, energy (ATP) dependence, Na+ dependence and interactions with a variety of compounds [3]. This suggested that TH uptake might be facilitated by different types of transporters. In recent years, this hypothesis was confirmed by the molecular identification of TH-transporting proteins [5]. These include the Na+/taurocholate cotransporting polypeptide [7], fatty acid translocate [8], multidrug resistance-associated proteins [9], amino acid transporters (reviewed in [10]) and members of the organic anion-transporting polypeptide (OATP) family (reviewed in [11]) and monocarboxylate transporter (MCT) family (reviewed in [12]).

Most studies report on cellular TH uptake, whereas far less is known about TH export from cells. This is surprising, because it is conceivable that not only influx but also efflux processes are required for optimal regulation of cellular TH availability. The majority of the TH transporters known currently accepts a wide variety of compounds and demonstrates a relatively low apparent affinity towards TH. To date, only OATP1C1 [13–15], MCT8 [16] and MCT10 [17] are reported to have high affinities for iodothyronines. The relative contribution of low-affinity versus high-affinity TH transporters to the transport of TH in vivo is unknown currently.

High-affinity transporters OATP1C1 and MCT10

The human SLC01C1 gene encodes the OATP1C1 protein, which comprises 712 amino acids and 12 putative transmembrane domains (TMDs). It is highly expressed in brain capillaries of rats and mice [14,15,18]. Although the particular cell types are unknown, OATP1C1 is distributed widely in the human brain [13]. OATP1C1-expressing cells show preferential transport of T4 and rT3 [13–15]. These studies suggest an important role for OATP1C1 in T4 transport across the blood–brain barrier. However, no patients with OATP1C1 mutations or knockout (KO) animal models have been reported so far. Thus, the precise in vivo function of OATP1C1 remains to be elucidated.

Because iodothyronines are basically composed of two tyrosine residues, it is feasible that a T-type amino acid transporter (TAT), which mediates transport of aromatic amino acids, is also involved in TH transport. Specific interactions between transport of T3 and tryptophan have been described, supporting this view [19,20]. Recently, one such transporter (TAT1) was cloned and reported to transport aromatic amino acids, although not T3 or T4 [21,22]. Its amino acid sequence indicates that it belongs to the MCT family; it is also named MCT10 (or solute-carrier family 16 member 10 (SLC16A10)).

We retested the possible involvement of MCT10 in TH transport and demonstrated substantial uptake of T3 and T4 by cells transfected with human MCT10 [17].

Corresponding author: Visser, T.J. (t.j.visser@erasmusmc.nl).
negative findings with respect to TH transport by MCT10 in previous reports might be explained by the high ligand concentration used and the subsequent supersaturation of the transporter in these studies. MCT10 is distributed widely, including the entire intestine, kidney, liver and placenta [21–23]. Recently, it was reported that a common polymorphism in the 3’-UTR region of MCT10 is not associated with altered serum TH levels [24]. No other studies investigating associations of aromatic amino acid or TH levels with polymorphisms or mutations in MCT10 have been published as yet. Investigations of MCT10 null mice would probably provide valuable insights into the precise physiological role of MCT10 in the transport of aromatic amino acids and TH.

**Identification and function of MCT8**

The human (h)MCT8 (SLC16A2) gene is located on the X-chromosome (at Xq13.2) and contains six exons. Its homology to the MCT family justifies its classification, although only MCT1–4 and MCT6 are known to transport monocarboxylates [12]. hMCT8 encodes two hMCT8 proteins of 613 and 539 amino acids, depending on which of the two putative translation-start sites (TLSs) is used. It is unknown currently whether there are two human MCT8 proteins expressed in vivo and, if so, whether they are subject to differential expression and regulation. Non-primate MCT8 genes lack the first TLS but are homologous with hMCT8 downstream from the second TLS [5]. MCT8 has 12 putative transmembrane domains and a N-termi-nus that is enriched in proline (P), glutamic acid (E), serine (S) and threonine (T) residues (abbreviated as PEST domain), which is why MCT8 was named XPCT (X-linked PEST-containing transporter) previously. Proteins containing PEST sequences often undergo rapid degradation [25]. It is unclear if this is relevant for MCT8.

More than a decade after characterization of the hMCT8 gene, rat MCT8 was identified as a specific and active TH transporter [16]. Oocytes injected with rat MCT8 cRNA showed a rapid uptake of the iodothyronines T4, T3, rT3 and T2 but not of sulfated iodothyronines, aromatic amino acids or monocarboxylates. Recently, the functional characterization of hMCT8 was described [26]. Cells transfected with hMCT8 cDNA displayed a marked T3 and T4 uptake but there was little effect on rT3 or T2 uptake. Cells cotransfected with hMCT8 and one of the deiodinases exhibited a significant increase in TH metabolism compared with cells transfected with hMCT8 or D3 alone. (a) Experimental model of T3 metabolism. MCT8, which is expressed at the plasma membrane, facilitates T3 uptake. D3, which is expressed intracellularly, catalyzes the conversion of T3 to T2 and T2 to T1. The metabolites T2 and T1 are exported into the incubation medium by as yet unidentified transporter proteins. The amount of T2 and T1 serves as a measure of intracellular T3 metabolism. hMCT8 and hCRYM was diminished significantly. These findings substantiate the concept that MCT8 is not only important for uptake but also for export of TH.

**MCT8 expression**

MCT8 shows a broad tissue distribution in all species studied. In situ hybridization studies revealed that MCT8 mRNA is expressed significantly in mouse liver, kidney, thyroid and brain [6,27]. In mouse brain, MCT8 mRNA is expressed predominantly in the choroid plexus of the ventricles and in the neo- and allo-cortical regions [28]. In rats, the MCT8 protein has been detected in heart and brain [16,29].

In humans, MCT8 is found in many tissues, in particular in liver and heart [30]. Expression of MCT8 mRNA and MCT8 protein in human placenta shows an increase during gestation [31]. MCT8 mRNA is upregulated in placentae associated with intrauterine growth retardation during the early third trimester of pregnancy, suggesting a compensatory mechanism to increase TH transport. MCT8
is also localized clearly in neurons of the paraventricular, supraoptic and infundibular nuclei of the hypothalamus and in glial cells of the ependymal lining of the third ventricle and median eminence [32]. In the human pituitary, the folliculostellate cells, rather than the thyroid-stimulating hormone (TSH)-producing cells, show MCT8 expression [33]. It is assumed that these sites are involved in the negative-feedback control of TSH-releasing hormone (TRH) in the hypothalamus and TSH in the pituitary, respectively, by TH.

Role of MCT8

The biological importance of MCT8 for brain development became apparent when mutations therein were associated with X-linked psychomotor retardation and elevated T3 levels (see below) [34,35]. The tight spatiotemporal regulation of TH during brain development is supposed to be controlled locally by functional units of astrocytes and neurons. Mainly based on immunohistochemical studies, this process is thought to involve at least the following steps (Figure 2). First, T4 (and a smaller amount of T3) is transported across the blood–brain barrier by OATP1C1. Second, T4 is taken up by astrocytes by an as-yet-unknown transporter. Third, T4 is converted to T3 by D2. Fourth, the biologically active T3 is released from the astrocytes by another unidentified transporter. Fifth, neuronal uptake of T3 is facilitated by MCT8. Sixth, T3 exerts its genomic action by binding to its nuclear receptor. Finally, T3 is degraded by D3 to T2 and both T3 and T2 might also leave the cells through MCT8. Too low or too high local TH concentrations might lead to abnormal TH signaling and might eventually result in abnormal brain development.

In addition to its role in brain development, MCT8 has been implicated in the differentiation of embryonic stem cells into neural cells [36]. So far, only iodothyronines have been shown to be ligands for MCT8. However, this does not preclude a role of MCT8 in the transport of other crucial ligands for brain development.

Patients with MCT8 mutations

It has been recognized that clinical features of patients with MCT8 mutations resembled those of Allan–Herndon–Dudley syndrome (AHDS) patients. Indeed, MCT8 mutations were found in all AHDS families tested, thereby providing a molecular basis for a syndrome already described in 1944 [37]. Affected males show a homogeneous neurological phenotype (Table 1 and reviewed in detail in [38]). There is a generalized low muscle tone with an inability to hold the head up, which usually progresses to spasticity. In addition, AHDS patients display episodic involuntary movements, which occur spontaneously or are triggered by stimuli. Most of the patients are unable to sit upright, crawl, stand or walk. Development of speech is absent in most affected individuals. However, in a few families, motor and speech development are somewhat less impaired, resulting in limited walking and verbal communication. All patients have a severe mental retardation with IQs below 40. Females with heterozygous MCT8 mutations do not express phenotypic abnormalities.

To date, mutations in MCT8 have not been localized to hotspot regions but are spread over the entire coding region of the gene. The identification of more than 20 affected families in recent years indicates that mutations in MCT8 are not an uncommon cause of X-linked mental retardation. It is clear that many of the mutations, such as

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Figure 2. Model for the local control of T3 availability in the brain. T₄ is transported through the blood–brain barrier (BBB) by OATP1C1 (dark blue). Subsequently, T₄ is taken up by astrocytes through an unknown transporter (?) and activated by D2. After T₃ export from the astrocyte through an unidentified transporter (?), MCT8 (red) facilitates T₃ uptake into the neuron. Neuronal T₃ interacts with its nuclear receptor, thyroid hormone receptor α (not shown), and results in the transcrption of various genes and the consequent generation of proteins. Neurons also express D3 for conversion of T₃ to T₂, thereby terminating T₃ activity. Reproduced from [28], with publisher’s permission.
large deletions and truncating mutations, are devastating for the function of the MCT8 protein. The effects on MCT8 function are less obvious with amino acid substitutions, deletions or insertions. Therefore, different mutations have been introduced into MCT8 cDNA by site-directed mutagenesis and have been tested functionally [6,39]. This was done by (co)transfecting JEG3 cells, which show little expression of endogenous MCT8, with wild-type or mutant expression of endogenous MCT8, with wild-type or mutant mutants. The effects on MCT8 function are less obvious with amino acid substitutions, deletions or insertions. Therefore, different mutations have been introduced into MCT8 cDNA by site-directed mutagenesis and have been tested functionally [6,39]. This was done by (co)transfecting JEG3 cells, which show little expression of endogenous MCT8, with wild-type or mutant expression of endogenous MCT8, with wild-type or mutant mutants.

In contrast to wild-type MCT8, transport and metabolism of T3 is absent completely with most MCT8 mutants (Table 1). However, the Leu683Pro, Leu434Trp, Ser194Pro and Arg271His mutants show significant residual activity. Interestingly, most patients in the families with Leu683Pro and Leu434Trp mutations had developed some walking and speech capacities. Additionally, males with the Ser194Pro mutation were able to walk. These observations suggest that diverse mutations affect MCT8 function differentially and might be the cause of minor phenotypic variations.

Patients with MCT8 mutations have abnormal thyroid function tests. TSH levels are approximately doubled compared with non-carriers [6]. Mean serum T4 and free T4 levels show a 40% decrease compared with healthy controls and rT3 values are diminished to 36% of control levels [6]. The most characteristic finding is markedly elevated T3 levels. Table 1 shows a 2.3-fold increase in T3 levels of studied MCT8 patients. In heterozygous (female) carriers, TSH levels are comparable to familial non-carriers [6,40]. However, other TH values seem to be intermediate between patients and non-carriers.

**MCT8 KO mice**

Recently, two different MCT8 KO mouse models were generated to gain insight into the mechanisms underlying

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**Table 1. Clinical, molecular and functional characteristics of MCT8 patients**

<table>
<thead>
<tr>
<th>Family</th>
<th>Gene mutation</th>
<th>Protein mutation</th>
<th>Serum T3 (fold increase versus controls)</th>
<th>Axial hypotonia</th>
<th>Absent speech</th>
<th>Never walked</th>
<th>T3 uptake (% versus controls)</th>
<th>T3 metabolism (% versus controls)</th>
<th>Protein expression (% versus controls)</th>
<th>Refs</th>
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<td>1/1</td>
<td>0*</td>
<td>0*</td>
<td>0*</td>
<td>[34]</td>
</tr>
<tr>
<td>2</td>
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<td>Ala224Val</td>
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<td>1/1</td>
<td>1/1</td>
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<td>0.0</td>
<td>+</td>
<td>[34,39]</td>
</tr>
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<td>0</td>
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<td>0*</td>
<td>0*</td>
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<td>0*</td>
<td>0*</td>
<td>[35]</td>
</tr>
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<td>2/2</td>
<td>2/2</td>
<td>8.6</td>
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</tr>
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<td>1/1</td>
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<td>2/2</td>
<td>2/2</td>
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<td>–3.5</td>
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<td>2/2</td>
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<td>0*</td>
<td>0*</td>
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<td>0*</td>
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<td>2.8</td>
<td>1/1</td>
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<td>1/1</td>
<td>2.4</td>
<td>–3.5</td>
<td>+</td>
<td>[6,39]</td>
</tr>
</tbody>
</table>

**Abbreviations:** del, deletion; Ex, exon; ins, insertion; NR, not reported; 0: absent; +: moderate; ++: normal; x/x: number affected/number with mutations.

*Presumed inactive.

**Brain**

<table>
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<tr>
<th>Tissue/serum</th>
<th>Measurement</th>
<th>Study 1</th>
<th>Study 2</th>
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<td>Dumitrescu et al.</td>
<td>Trajkovic et al.</td>
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<tr>
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<td>D2 mRNA</td>
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</tr>
<tr>
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<td>D3 activity</td>
<td>ND</td>
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<td></td>
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*All values represent significant fold changes in male MCT8 KO mice compared with wild-type mice.*
KO animals is associated with low brain D3 activity, which is regulated positively by TH. Trajkovic et al. also studied whether MCT8 inactivation results in neuronal abnormalities [27]. Although transcript levels of the TH-responsive RC3 gene are decreased mildly in the striatum, histological examination of cerebellar Purkinje cells, which normally produce MCT8, did not detect any abnormalities.

Additionally, different aspects of the hypothalamus—pituitary—thyroid axis were investigated in MCT8 KO mice. TRH transcript levels are increased strongly in the hypothalamic paraventricular nucleus (PVN) neurons in MCT8 KO mice. The elevated TRH expression is suppressed by T4 but not by T3 administration, indicating that these neurons are able to respond to locally produced T3. In contrast to the ‘hypothyroid’ state in the hypothalamus, the pituitary appears to be ‘euthyroid’ because transcript levels of TH-responsive genes were not altered in MCT8 KO mice [27]. However, the pituitary in the MCT8 KO animals is relatively insensitive to T3. Only administration of high T3 concentrations is able to suppress TSH in MCT8 KO animals rendered hypothyroid.

The most remarkable finding in these MCT8 KO animals is the absence of neurological disturbances, despite the low levels of T4 and T3 in the brain. This might be explained in different ways. First, brain development in mice might respond differently to TH deficiency than in humans. Second, the lack of MCT8 might be compensated sufficiently by other TH transporters in mouse brain but not in human brain, securing a relatively normal development in the mouse. Third, human MCT8 might transport other ligands, which are essential for normal human brain development. Fourth, the putative long MCT8 protein in humans might have other functions in addition to the short MCT8 protein, the only form present in mice.

Thus, although MCT8 KO mice are a suitable tool with which to study TH abnormalities, it remains a challenge to unravel the precise mechanisms involved in the pathogenesis of the psychomotor retardation in human patients with MCT8 mutations.

Pathophysiology of MCT8 mutations
Integrating the findings in humans and mice with MCT8 mutations might lead to the following considerations. The modestly increased serum TSH levels in patients seem to fit with the low free T4 levels, although, in view of the strongly elevated serum T3, the TSH levels appear inappropriately high. Studies in the MCT8 KO mice indicate a relative TH insensitivity in the hypothalamus and pituitary. The inappropriate TSH levels in human MCT8 patients correspond with a partial hypothalamic and pituitary TH resistance. The presence of MCT8 in human hypothalamus and pituitary fits with this hypothesis [32,33].

In keeping with the assumed function of MCT8 in neuronal T3 uptake, it is fully understandable that MCT8 mutations result in a diminished intracellular T3 concentration. Considering the crucial role of TH in normal brain development, it is conceivable that neurological defects will be the consequence of this neuronal T3 deprivation. It is unknown currently whether all T3-dependent neurons express MCT8. Therefore, it cannot be excluded that certain types of neurons express other prominent T3 transporters, instead of or in addition to MCT8. Depending on the presence of additional transporters, MCT8 might function primarily in the import or in the export of T3. In the former case, inactivation of MCT8 will result in decreased intracellular T3 levels and, in the latter case, in an increased intracellular T3.

Changes in deiodinase activities contribute to the abnormal TH levels in subjects with MCT8 mutations. The accumulation of T3 might be the result of blocking T3 entry into D3-expressing cells, which in turn leads to a decrease in T3 clearance. This would be followed by an increase in renal and hepatic D1 activities and consequent T3 production, which further stimulates T4 to T3 conversion. The increased D1 activity might also contribute to decreased circulating T4 and rT3 concentrations. Recently, it was shown that the T3:T4 ratio increases with age in MCT8 KO mice, thereby underscoring the prominent role for D1 in the origin of the TH abnormalities [42].

It is feasible that the liver in MCT8 patients is in a hyperthyroid state, as is the case in MCT8 KO mice, because sex hormone-binding globulin (SHBG) concentrations are increased markedly in serum [6]. Because SHBG production in the liver is regulated positively by T3, SHBG levels are indicative for the TH status in the liver. The hyperthyroid state in the liver is explained by the elevated serum T3 levels and a presumed lack of importance of MCT8 for hepatic T3 uptake. If MCT8 in liver is more important for T3 efflux, its inactivation might further increase intracellular T3. The low muscle and fat mass in MCT8 patients might be the result of tissue ‘wasting’ because these tissues are in a hypermetabolic state owing to their exposure to high T3 levels. Apparently, muscle and fat do not require MCT8 for TH uptake.

In conclusion, although it is apparent that MCT8 has a crucial role in proper brain development, the contribution of MCT8 to TH transport in other tissues is less clear. The exact mechanisms that have a role in the generation of tissue-specific hypo- or hyperthyroidism remain to be elucidated.

Treatment of MCT8 patients
Currently, the therapeutic options for MCT8 patients are limited. The harmful effects of TH deprivation on early brain development are almost certainly irreversible. Therefore, postnatal TH treatment is expected to have limited positive consequences. Only mutations that inactivate MCT8 partially might benefit from TH therapy. Theoretically, T3 analogues that are taken up by cells in which MCT8 is disrupted might also have a place in the treatment of MCT8 patients. Supportive therapy, such as appropriate diet to prevent aspiration, as well as anticonvulsant therapy, might alleviate some of the secondary somatic problems. Although treatment options are limited in MCT8 patients, the detection of MCT8 mutations is important for providing a diagnosis to family members, carrier identification and prenatal diagnosis.

Conclusion
TH is essential for the normal development of various tissues, especially the brain. Proper intracellular TH concentrations are required for normal TH action and
metabolism. Therefore, TH transport across the plasma membrane is crucial. Several TH transporter families have been identified, however, only MCT8, MCT10 and OATP1C1 have been shown to be specific TH transporters so far.

Whereas the physiological significance of MCT10 and OATP1C1 remains to be further investigated, an important function of MCT8 in normal brain development has been established in recent years. Mutations in MCT8 are associated with high T3 levels and severe psychomotor retardation. MCT8 KO mice have been generated, which lack neurological abnormalities but imitate the TH abnormalities in MCT8 patients perfectly. Although the MCT8 KO mice have provided interesting insights, the precise mechanisms underlying this dramatic disorder in humans need to be clarified.

The progress made in the molecular identification of TH transporters in recent years should be continued by investigating cellular TH transport processes. Not only TH influx, but also export, deserves attention in the forthcoming years. Undoubtedly, novel syndromes caused by defects in TH transporters will be recognized and linked to TH insensitivity. Continuing research in the complex world of TH transport in and out of cells promises a fascinating future.

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